

(12) **UK Patent Application** (19) **GB** (11) **2 136 123 A**

(43) Application published 12 Sep 1984

(21) Application No **8405603**

(22) Date of filing **2 Mar 1984**

(30) Priority data

(31) **8306055** (32) **4 Mar 1983** (33) **GB**

(51) INT CL³

G01N 33/15 B01F 1/00

(52) Domestic classification

G1B BG CD

U1S 1310 1463 G1B

(56) Documents cited

None

(58) Field of search

G1B

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(54) **Dissolution Testing Machine**

(57) A dissolution testing machine has a container for a liquid and a holder for pellets, means supporting the holder within the container and drive means enabling the holder to be reciprocated via its support means so that solvent flushes into and out of the holder.

The holder may be a mesh tube, or a solid walled tube, closed at both ends by an apertured member. A set of containers may receive the holder successively, each container containing a solvent of the same or different characteristics.

The container or containers may be supported in a temperature-controlled bath.

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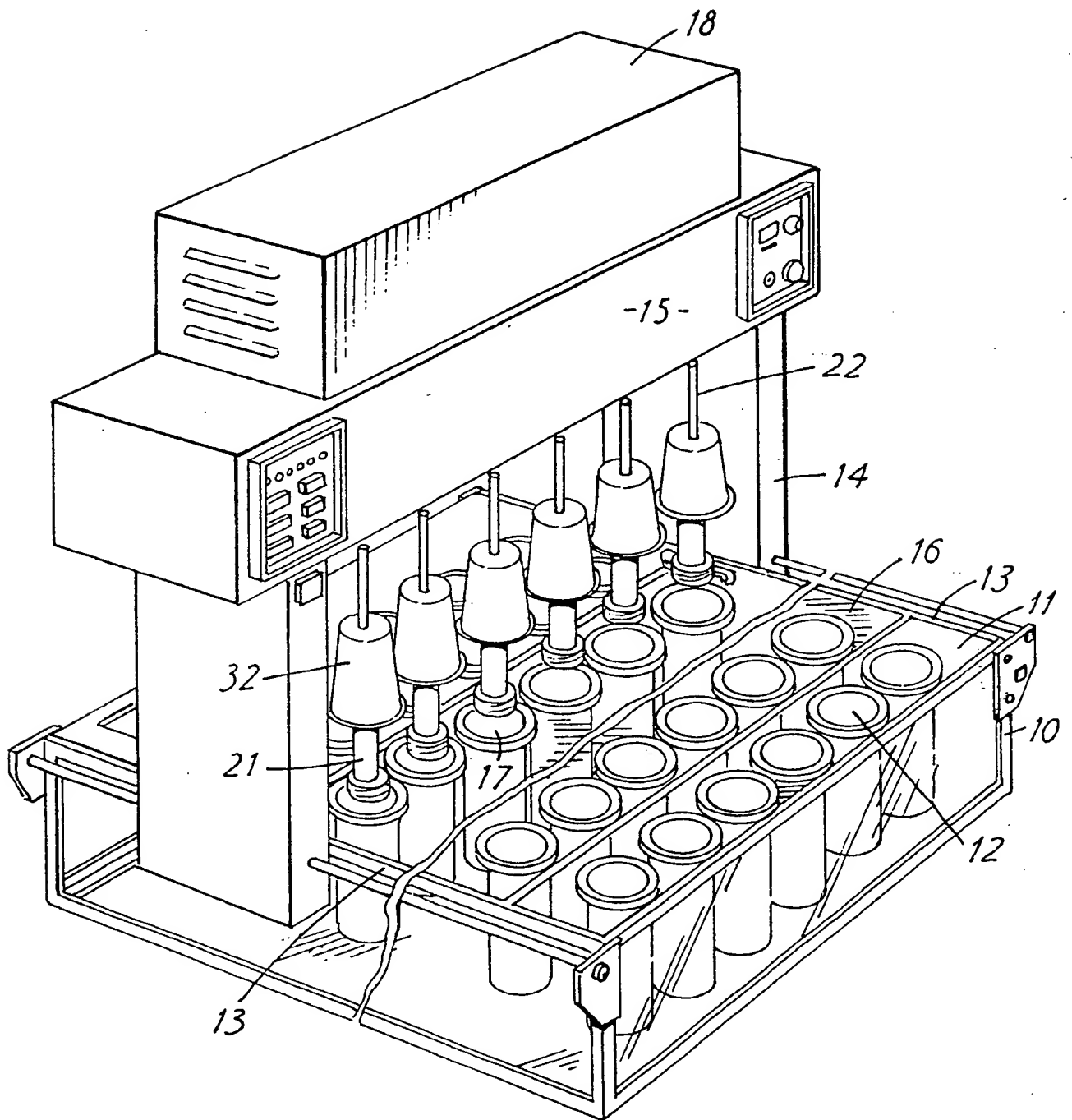
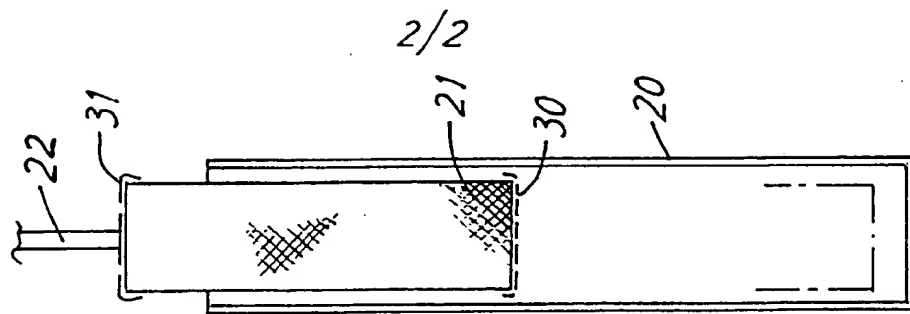
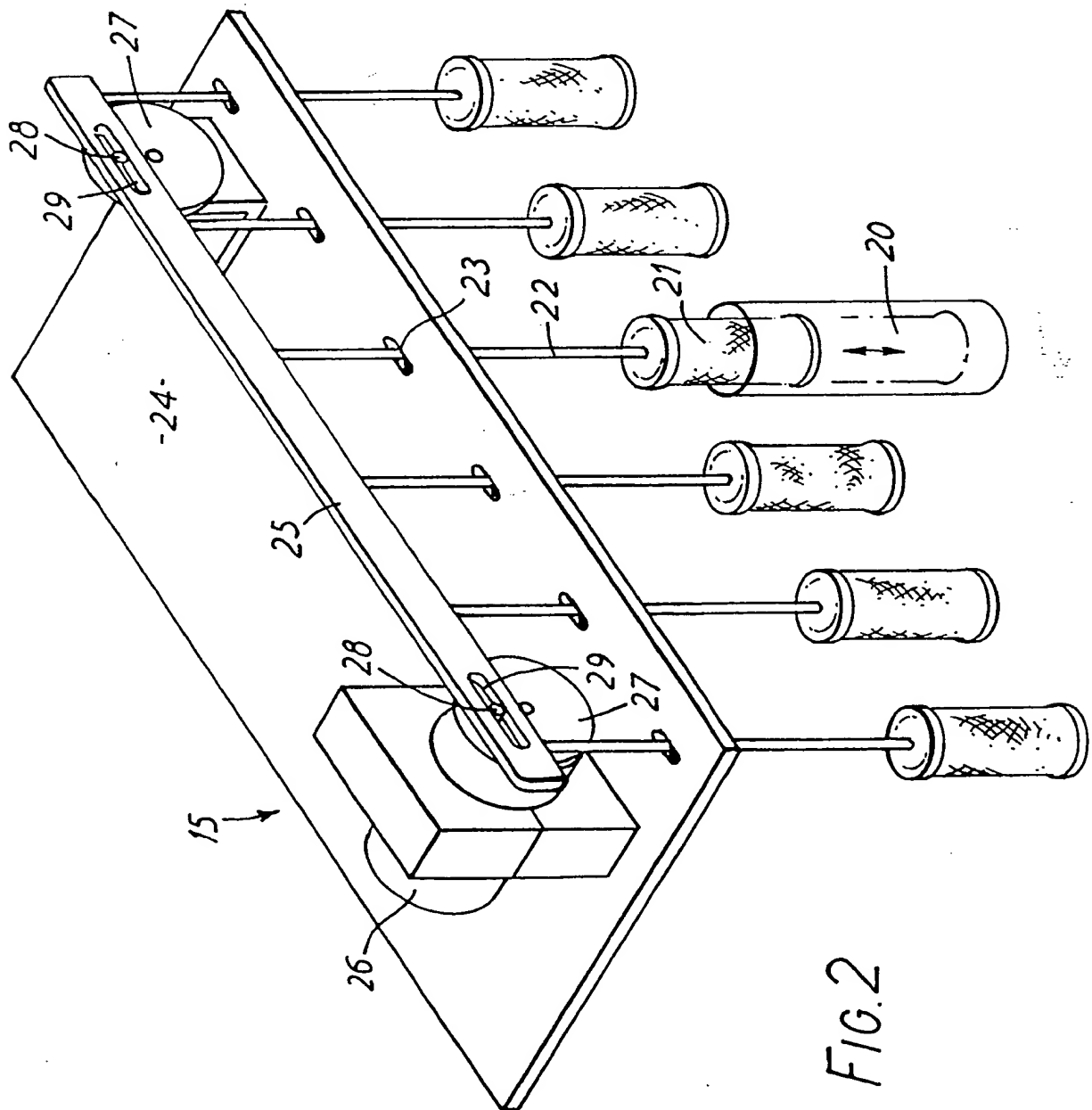


FIG. 1



SPECIFICATION

Dissolution Testing Machine

This invention relates to dissolution testing machines, capable of measuring the dissolution rate of chemicals from tablets or pellets. Such machines are, in particular, used in the pharmaceutical industry in connection with measuring the controlled rate of release of drugs.

In the past, two main standard methods have been used to conduct experiments on the rate of release of chemicals. In the first, the tablets, capsules, pellets or the like (hereinafter called 'pellets'), are placed in the bottom of a standard container, and a paddle of standard shape is rotated about a vertical axis in a standard position in the container. However, the tendency is for the pellets to form a heap in the bottom of the container directly below the paddle, and the solution formed tends to maintain a gradient with the highest concentration at the bottom and the lowest at the top. Although standardised, as between tests such an apparatus does not provide a true indication of rate of dissolution of the pellets when taken internally by a patient.

In the second method, the pellets are placed inside a perforated basket of generally cylindrical shape, which basket is itself rotated about its central longitudinal axis in the liquid. However, the tendency then is to form a film of chemical in solution around the pellets, with a higher concentration of solution within the basket than outside it. An increase in the speed of rotation may increase the dissolution rate, but may also cause abrasion of the pellets by the basket mesh, which thus falsifies the results in an opposite direction.

A third unofficial method employs a rotating bottle, in effect mounted on an arm of a rotating wheel in a vertical plane, so that the bottle is tipped upside down once in every revolution. However, since the bottle must be liquid tight during this operation, it becomes very difficult to extract samples for testing at different time intervals, and the process is inconvenient and labour intensive.

The invention aims to provide a machine which allows reproducible testing of the dissolution rate of pellets, permits sampling either manually or automatically, and which does not suffer from the "retarding" effects common in known machines due to concentration gradients in the solvent due to inefficient flushing of the solvent over the pellets.

Accordingly, the invention proposes a dissolution testing machine comprising a container for a liquid and a holder for pellets means supporting the holder within the container, and drive means enabling the holder to be reciprocated via its support means so that solvent flushes into and out of the holder.

Such a machine preferably employs an elongated cylindrical container, similar to a test tube, and a cylindrical holder coaxial within the container and reciprocated along that axis. The holder may be a mesh basket, or a solid tube closed at its ends with mesh.

The invention also proposes a method of testing the dissolution of chemicals, wherein the chemicals are placed in a holder which is open at least at top and bottom and said holder is reciprocated up and down in a container of solvent in standard conditions.

In a preferred method, said holder is moved successively from one to another of a plurality of containers, each container holding a solvent of the same or different characteristics.

In order that the invention shall be clearly understood, an exemplary embodiment of a machine will now be described with reference to the accompanying drawings, in which:

Figure 1 shows an overall schematic view of the machine according to the invention;

Figure 2 shows the support means and drive means, and

Figure 3 shows a container and a mesh basket holder for the machine.

In Figure 1, a frame 10 supports a temperature controlled bath (not shown) which almost completely fills it. The top of the frame is covered by a matrix or framework 11 which defines a plurality of positions arranged in rows 16 and columns 17, each position 12 being designed to receive a glass container, approximately the shape and size of a large test tube. The bath is maintained at a constant temperature of approximately 37 degrees, thus maintaining the contents of the tubes at that temperature. A bridge structure 14 straddles the frame 10 and is movable by sliding along guide members on two upper sides 13 of the frame. Thus, the bridge 14 can be brought successively to positions above each of the rows of containers. The bridge 14 supports six mesh baskets which are suspended below it, and also drive means 15 for controlling movement of the baskets. A control unit 18 controls the operation of the machine.

Figure 2 shows an enlarged and a more detailed view of the drive means and baskets supported on the bridge 14. A set of six glass containers 20 supported in the heated bath are arranged in the first row (only one container is shown). Directly above each container is suspended a small mesh basket 21, approximately 10 centimetres long and 2.5 cm in diameter. Each basket 21 is supported on a rod 22 which extends through a hole 23 in a support plate 24, and is fixed on a transverse bar 25. A motor 26 drives synchronously two discs 27 at a speed of between 5 and 50 r.p.m., preferably about 20 r.p.m. A pin 28 on each disc engages slots 29 in the beam 25, so that rotation of the discs 27 causes the whole structure supporting the series of baskets 21 to move gently up and down.

The nature of the container and basket can be seen from Figure 3. The container 20 is made of glass and has the shape of a right cylinder with an open top. The mesh basket 21 is made preferably of

metal and is open at both top and bottom. The mesh may have any desired hole size. The bottom of the mesh basket is closed by a layer of gauze fabric 30 held by a small elastic band. The reason for this is that as the basket is reciprocated, the pellets will not be abraded by hitting the gauze. At the top, the basket is closed by a perforated plastic cap 31 which clips onto a bead on the top edge of the basket.

5 The rod 22 is fixed directly to the cap 31. A splash cover 32 (Figure 1) may be provided. The materials used must be inert to both the solvent and the chemicals of the pellet, and must not absorb these substances. 5

In use, pellets to be dissolved are placed in the baskets, and the containers 20 are filled approximately three-quarters with a solvent, sufficient so that the pellets are not raised right out of the solvent. The up and down movement causes the solvent to be flushed in and out of the baskets in a controlled fashion, so as to produce dissolution of the pellets. The pellets are levitated with each downward stroke. 10

In an alternative, the holder may be a solid glasstube which cannot abrade the pellets, open top and bottom. These are then covered by mesh discs or fabric and held in position by a perforated plastic cap. Any suitable construction can be used which allows easy insertion of pellets, and easy liquid flow. The perforations of the cap and the mesh size of the disc or fabric may be chosen according to need. For example, very fine holes may be required for retard tablets which disintegrate before they dissolve. 15

Since the controlled experiments normally to be carried out with the machine requires a series of tests of varying duration and with solvents of varying characteristics or concentrations, the machine is arranged so that the bridge 14, after performing one set of tests on the pellets in the first row of containers, is moved along the framework 10 until the baskets are aligned above the second row of containers. These containers may contain the same solvents at a different concentration, or a different solvent, and a further test can be performed for the same or a different time period. The dissolution rate in the first row of containers can be determined from the solution strength then remaining in those containers. Thus, the machine shown has the capacity to perform simultaneously six tests using the same or different pellets in different containers, and to repeat this operation six times in different solvents, or for different periods. Between each test, the baskets are raised to their highest position and the bridge 14 indexed sideways. 20 25

In a typical test, a single solvent is used in all cases, but with a different pH value in each row. The six successive tests would then be as follows: 30

Row	1	2	3	4	5	6
pH	1.5	4.5	6.9	6.9	7.2	7.5
Time	1 hr	1 hr	2 hrs	2 hrs	2 hrs	4 hrs

Such a test would approximate to the effect of gastric juices acting on a capsule swallowed by a person, and would be of use in determining the likely effects of swallowing a capsule containing a multitude of pellets of different solubilities intended to provide drug release throughout a period of 12 hours. 35

The measurement of the solution strengths left in each of the six containers forming one column and representing one set of test results can be performed in a number of ways. They can be tested manually as the sequence proceeds. Or the drive means and baskets can be replaced by a separate 'head' consisting of a set of six dip tubes which can sample and test all six containers of one row. By indexing the head sideways using the bridge 14, the dip tubes can be lowered into successive rows of containers and set of readings produced for each column by each dip tube. Such a successive sampling can be carried out after completion of the actual dissolution tests. 40

Alternatively, the dip tubes could be mounted on the same head as the baskets, and arranged to sample the solutions one row behind the row currently receiving the pellets. In this case, the bridge 14 would need to index one step more than the numbers of rows of containers. 45

The control unit 18 may be manually controlled or micro-processor operated, so that all the indexing and timing can be pre-determined by hard or soft programming. This can also be applied to the subsequent sampling. 50

The invention can be applied to less complex machines than this, which is designed for batch sampling. A machine having one basket mounted on a head which is rotatable in the middle of a circular array of containers is also envisaged. Control may again be manual or automatic.

CLAIMS

1. A dissolution testing machine comprising a container for a liquid and a holder for pellets, means supporting the holder within the container and drive means enabling the holder to be reciprocated via its support means so that solvent flushes into and out of the holder. 55

2. A machine as claimed in claim 1, comprising a set of containers, in which said means can be moved so that the holder is supported successively in each container of the set.

3. A machine as claimed in claim 2, wherein said set of containers is located in a temperature controlled bath.
4. A machine as claimed in any preceding claim, wherein each said container is tubular.
5. A machine as claimed in claim 4 wherein each said holder is a solid walled tube, closed top and bottom by an apertured member. 5
6. A machine as claimed in claim 4 wherein each said holder is a mesh-walled tube, closed top and bottom by an apertured member.
7. A machine as claimed in claim 5 or 6 wherein the bottom of each holder is soft and/or resilient so that pellets therein are not abraded thereby.
- 10 8. A machine as claimed in any of claims 2 to 7 wherein said containers are arranged in a row and said means can be moved linearly from one to the next. 10
9. A machine as claimed in claim 8 wherein there are a plurality of sets of containers and a corresponding plurality of holders, whereby a plurality of dissolution tests can be carried on simultaneously.
- 15 10. A machine as claimed in any of claims 2 to 7 wherein a movable frame above the containers carries the drive means, the support means and the holders. 15
11. A machine as claimed in any of claims 2 to 10 wherein a sampling tube can be arranged adjacent each said support means for drawing off a sample of liquid in a container either from the container in which the holder is supported or from an adjacent one of the set.
- 20 12. A machine as claimed in claim 11 when appendant to claim 10, wherein the movable frame can be moved through a number of positions equal to one more than the number of containers in the set. 20
13. A machine as claimed in any of claims 2 to 7 wherein said set are arranged in a circle and said means can be moved in an arc from one to the next.
- 25 14. A method of testing the dissolution of chemicals, wherein the chemicals are placed in a holder which is open at least at top and bottom and said holder is reciprocated up and down in a container of solvent in standard conditions. 25
15. A method as claimed in claim 14 wherein said holder is moved successively from one to another of a plurality of containers, each container holding a solvent of the same or different characteristics. 30